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TITLE: Process for coating stents

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Coating may be formulated by mixing one or more therapeutic agents with the coating polymers in a coating mixture. The therapeutic agent may be present as a liquid, a finely divided solid, or any other appropriate physical form. Optionally, the mixture may include one or more additives, e.g., nontoxic auxiliary substances such as diluents, carriers, excipients, stabilizers or the like. Other suitable additives may be formulated with the polymer and pharmaceutically active agent or compound. For example hydrophilic polymers selected from the previously described lists of biocompatible film forming polymers may be added to a biocompatible hydrophobic coating to modify the release profile (or a hydrophobic polymer may be added to a hydrophilic coating to modify the release profile). One example would be adding a hydrophilic polymer selected from the group consisting of polyethylene oxide, polyvinyl pyrrolidone, polyethylene glycol, carboxymethyl cellulose, hydroxymethyl cellulose and combination thereof to an aliphatic polyester coating to modify the release profile. Appropriate relative amounts can be determined by monitoring the in vitro and/or in vivo release profiles for the therapeutic agents.

This Example describes the preparation of coated stents containing various

levels of rapamycin for in vitro drug release testing.

0.06 gms of Rapamycin was dissolved into 0.8 gms of 15% CAP/GLY solution in 1,1,2 TCE. The resulting coating solution contained 33.3% w/w drug on a dry, solid-only basis. Stents were coated by the method described in Example 1 and the coated stents were designated as 'Std 33%'.

0.015 gms of Rapamycin was dissolved into 0.5 gms of 18% CAP/GLY solution in 1,1,2 TCE. The resulting coating solution contained 14.3% w/w drug on a dry, solid-only basis. Stents were coated by the method described in Example 1 and the coated stents were designated as '14%'

0.028 gms of rapamycin was dissolved into 0.5 gm of 18% CAP/GLY solution in 1,1,2 TCE. The resulting coating solution contained 23.7% w/w drug on a dry, solid-only basis. Stents were coated by the method described in Example 1. The dip-coated stents were spray coated with polymer-only solution as described in Example 6. The final coated stents were designated as '24-TC%'

0.028 gms of rapamycin was dissolved into 0.5 gm of 18% CAP/GLY solution in 1,1,2 TCE. The resulting coating solution contained 23.7% w/w drug on a dry, solid-only basis. Stents were coated by the method described in Example 1. The dip-coated stents were spray coated with polymer-only solution as described in Example 6;

0.06 gms of rapamycin was dissolved into 0.8 gm of 15% CAP/GLY solution in 1,1,2 TCE. The resulting coating solution contained 33.3% w/w drug on a dry, solid-only basis. Stents were coated by the method described in Example 1. The dip-coated stents were spray coated twice with .epsilon.-caprolactone-co-lactide (Cap/Lac) solution as

described in Example 4.

The final coated stents were designated as '33-TC%'.

0.06 gms of rapamycin was dissolved into 0.8 gm of 15% CAP/LAC solution in 1,1,2 TCE. The resulting coating solution contained 33.3% w/w drug on a dry, solid-only basis. Stents were coated by the method described in example 1. The dip-coated stents were spray coated twice with polymer-only solution as described in Example 6 (except .epsilon.-caprolactone-co-lactide was used as the copolymer). The final coated stents were designated as '33-C/L TC%'.

This example describes the results of testing the in vitro drug release of rapamycin from coated stent.

Coated stents were prepared as described in Example 7 with varying concentrations of rapamycin were tested for the in vitro release of rapamycin into an aqueous ethanol solution. As is indicated in FIG. 7, the stents denoted by the diamonds had a primer coating and a base coating that contained rapamycin. The total weight of the coating and rapamycin on the each stent was approximately 450 .mu.g and contained 33 percent by weight of rapamycin. The coating was a copolymer of .epsilon.-caprolactone-co-glycolide (45:55 mole percent) applied by dip coating. The squares represent data points for stents having a primer coating and a base coating containing rapamycin. The total weight of the coating and drug was approximately 450 .mu.g, which contained 14 percent by weight rapamycin. The coating material was also a copolymer of .epsilon.-caprolactone-co-glycolide (45:55 mole percent) applied by dip coating. The triangles represent data points for stents that had a primer coating and a base coating containing rapamycin. A primer

coating and base coating (.epsilon.-caprolactone-co-glycolide 45:55 mole percent) were applied by dip coating the stent. A top coat of 200 .mu.g (.epsilon.-caprolactone-co-glycolide 45:55 mole percent) was then applied using an ultrasonic spray device. The total weight of the coating and rapamycin was 650-700 .mu.g, which contained 24 percent by weight rapamycin. The Xs represent data points for stents that had a primer coat and a base coating containing rapamycin. The primer coating and base coating (.epsilon.-caprolactone-co-glycolide 45:55 mole percent) were applied by dip coating the stent. A top coat of 100 .mu.g (.epsilon.-caprolactone-co-glycolide 45:55 mole percent) was then applied using an ultrasonic spray device. The total weight of the coating and rapamycin was 550-600 .mu.g, which contained 24 percent by weight rapamycin. The asterisk represents data points for stents that was coated with a primer, a base coat and two top coats. The primer coating and base coating (.epsilon.-caprolactone-co-glycolide 45:55 mole percent) were applied by dip coating the stents. A top coat of 100 .mu.g (.epsilon.-caprolactone-co-glycolide; 45:55 mole percent) was then applied using an ultrasonic spray device. The total weight of the coating and rapamycin was approximately 550 .mu.g, which contained 33 percent by weight rapamycin. The circles represent data points for stents that were dip coated with .epsilon.-caprolactone-co-lactide (40:60 mole percent). The stents were then top coated with an ultrasonic spray with approximately 100 .mu.g of .epsilon.-caprolactone-co-lactide. The total coating weighed about 550 .mu.g and contained 33 percent by weight rapamycin.

Each stent was placed in a 2.5 mL of release medium (aqueous ethanol; 15 percent by volume at room temperature) contained in a

13.times.100 mm culture tube. The tube was shaken in a water bath (INNOVA.TM. 3100; New Brunswick Scientific) at 200 rpm while maintaining ambient conditions. After a given time interval (ranging from 15 minutes to one day) the tubes were removed from the shaker and the respective stents carefully transferred to a fresh 2.5 ml Aliquot of release medium. The new tube was placed on the shaker and agitation resumed. A sample was removed from the aliquot, which had previously contained the stent and placed in a HPLC vial for determination of the rapamycin content by HPLC.

The goal of this study was to assess the rate of release of rapamycin from polymer-coated stents introduced in vivo into the coronary arteries of Yorkshire pigs. At various times after introduction of stents, the pigs were euthanized and the coronary arteries removed, the stents dissected free of the artery and analysed for rapamycin content using loading assay previously described. Through comparison with the amount of rapamycin contained on control, non-implanted stents, the in vivo rate of rapamycin release from the polymer coatings could be determined.

FIG. 7 illustrates a typical in vivo release curve for a stent coating consisting of 33% rapamycin in polycaprolactone-co-glycolide.

This preliminary study was conducted to assess the ability of rapamycin released from .epsilon.-caprolactone-co-glycolide copolymer-coated stents to inhibit intimal hyperplasia in vivo. Fourteen days after receiving rapamycin-loaded or control polymer coated stents, the male Yorkshire pigs were euthanized and the coronary arteries removed, the vessels

prepared for histological evaluation and analysed for the amount of intimal growth. Through comparison control metal stents and stents containing polymer only, the in vivo ability of rapamycin to prevent neointimal growth could be determined.

As can be seen in Table 1, local delivery of rapamycin to injured coronary arteries resulted in a significant ( $p < 0.05$ ) reduction in intima:media ratio in the 166 .mu.g treatment group and a small but non-significant reduction in the 32 .mu.g treatment group when compared with the polymer and bare metal control groups. Rapamycin delivered from the GAP/GLY coating also resulted in non-significant dose-related decreases in neointimal area in both the 32 .mu.g and 166 .mu.g treatment groups. The percent diameter stenosis as assessed by angiography was also significantly reduced in the 2 rapamycin treatment groups when compared to the CAP/GLY group, although the reduction in this parameter from the metal control was small and non-significant. Never-the-less, in this preliminary 14 day study, these data suggest that local release of rapamycin from a biodegradable hydrophobic polymer coating may be capable of limiting the amount of neointimal proliferation which occurs as a result of stent deployment.

TABLE 1				Histology	
Angiography	Intima/ Intimal % Diameter (mm.sup.2)	B/A Stenosis	Treatment	Media ratio	Area
Ratio					Metal Control
0.90	+- 3.65				
+- 24.8	+- 3.9.sup.1	1.27	+- (n = 10)	0.05	0.82
0.05	CAP/GLY (n = 8)				
0.91	+- 4.15	+- 38.0	+- 4.0	1.32	+- 0.11 0.23
0.04	CAP/GLY + 32				
.mu.g	0.75	+- 3.27	+- 21.6	+- 3.6.sup.1	1.23 +-.
<u>rapamycin</u>	(n = 10)				

0.04 0.16 0.03 CAP/GLY + 166 .mu.g 0.65 .+- . 2.87 .+- .  
 23.9 .+- . 2.3.sup.1  
 1.27 .+- . rapamycin (n = 8) 0.04.sup.1,2 0.31 0.05  
 .sup.1 p < 0.05  
 from CAP/GLY .sup.2  
 p < 0.05 from Metal Control All values are mean .+- .  
 sem. B/A ratio =  
 balloon to artery ratio, an index of the consistency of  
stent expansion from  
 group to group

	<b>Title</b>	<b>Current OR</b>	<b>Current XRef</b>
<b>1</b>	<b>Modified stent useful for delivery of drugs along stent strut</b>	<b>623/1.42</b>	<b>623/1.39</b>
<b>2</b>	<b>Process for coating stents</b>	<b>427/2.3</b>	<b>427/2.25; 427/2.28; 427/232; 427/235; 427/355</b>



	<b>Retrieval Classif</b>	<b>Inventor</b>	<b>S</b>	<b>C</b>	<b>P</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
<b>1</b>		<b>Wright, Carol et al.</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>2</b>		<b>Hossainy, Syed F. A. et al.</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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<b>2</b>	<input type="checkbox"/>	<input type="checkbox"/>	<b>US 6153252 A</b>	<b>20001128</b>	<b>16</b>

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